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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,488	05/11/2001	Chamsy Sarkis	ST98023A	8713

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EXAMINER	
VOGEL, NANCY S	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,488	SARKIS ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-58 are pending in the case.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 44, 47-49, 52 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record set froth in the office action mailed 9/23/03, slightly altered to take into consideration applicant's amendments to the claims filed 3/23/04, adding claims 44, 47-49, 52 and 56-58.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. They encompass pharmaceutical compositions comprising baculovirus containing any gene which may have therapeutic

use in the treatment of any neurological disorder, and methods of treating any disease of the nervous system comprising administering said baculovirus, and methods of expressing a therapeutic product by administrating a baculovirus vector in the central nervous system, i.e gene therapy. There are a large numbers of diseases encompassed by the term "disease of the nervous system", ranging from cerebral palsy, to Alzheimer's disease, to Parkinson's disease, etc. There are a large number of genes whose products may be therapeutic for said diseases.

The nature of the invention is very complex because it is compositions and methods that are to be used to treat illness, and the treatment method includes the administration of a foreign gene in vivo, i.e. gene therapy. The list of possible diseases to treat is very large and concerns treating very complex diseases, some of which have no known treatments.

The state of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997)389:239-242) and Palu et al. (J. Biotechnol. (1999) 68:1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239 1st paragraph ; Palu et al. p.1. Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. While these references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene deliver,

targeting and expression must be made before gene therapy becomes a useful technique. See Verma et al p.242, col. 2-3, ; Palu et al. pp 10-11.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2):1-3. Furthermore, it cannot be predicted whether the claimed method comprising administration of the recombinant baculovirus would result in appropriate expression levels, in appropriate cells, such that amelioration of neurological symptoms would result. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression. While the specification lists a large number of proteins and promoters that can be produced using the recombinant baculovirus, and shows in vitro and in vivo infection of cells with a recombinant baculovirus expressing a marker protein, there is no example of the treatment of a neurological disease, or guidance for such aspects as dosage, and method of administration, that would be required for effective treatment of any diseases of the nervous system.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a disease of the nervous system, one of skill I the art would have to determine the effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for the treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and host to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require ad large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the art of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require under experimentation by one of skill in the art to determine how to practice the claimed invention.

Applicants have stated that the rejection of claims 18, 25-27 and 30 under 112, first paragraph, set forth in the previous office action, is moot in view of the amendments to the claims. However, it is maintained that the rejection remains applicable to newly presented claims 44, 47-49, 52 and 56-58 for the reasons set forth above.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34-43, 45, 46, 50, 51, 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyce et al. (WO9812311).

This rejection is maintained for reasons of record set forth in the office action mailed 9/23/03, slightly altered to take into consideration applicant's amendments to the claims filed 3/23/04, canceling the previous claims and adding claims 34-43, 45, 46, 50, 51, 53-55.

Boyce disclose a recombinant baculovirus having a baculovirus envelope protein, comprising a gene encoding a heterologous protein operatively associated with a promoter, wherein said promoter is an eukaryotic promoter active in mammalian cells, and wherein the heterologous protein may be of therapeutic interest for the treatment of neurological disease (page 3 lines 8-31). The reference discloses that said gene may encode any protein of interest, including enzymes of the urea cycle (page 2, lines 4-20), nerve growth factors, HGPRT, tyrosine hydroxylase, dopadecarboxylase, brain-derived neurotrophic factor and basic fibroblast growth factor (page 3, lines 8-18), or any gene useful for treating a neurological disorder (page 5, lines 7-23). The reference discloses that any cell-type specific promoter may be used, such as neuron-specific enolase promoter, or tyrosine hydroxylase promoter (page 8 line 46- page 9 line 10, page 11, line 4-32). The reference discloses that the recombinant baculovirus may comprise an envelope protein which is foreign to a baculovirus, i.e. VSV (see page 3, lines 25 – page 4 line 4). The reference discloses that a signal sequence may be used for targeting of the gene product (page 8 line 46). The reference discloses cells, or implants, including

neurons, infected with said baculovirus (see page 9 line 11-26, page 18, lines12-21, page 21 last line – page 22 last paragraph, page 28, lines 35-44) .

Applicant has argued that Boyce et al. do not "prove the capacity of a recombinant baculovirus to infect and express an exogenous gene in a neural cell both in vivo and in vitro" (page 9 of the amendment) and further argue that Boyce do not disclose any in vivo results. However, it is maintained that Boyce et al. do teach the claimed baculovirus comprising a heterologous nucleic acid sequence operatively associated with a promoter active in neuronal mammalian cells, as set forth above, and therefore the vectors disclosed by Boyce meet all the limitations of the instantly rejected claims. Any properties such as ability to infect mammalian cells in vivo would be inherently possessed by the disclosed baculovirus vectors. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 34-43, 45, 46, 50, 51, 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyce et al. in view of Gritson et al. (Nucl. Acids Res. Vol. 25, No. 9, 1864 (1997), Li et al. (Biochem. J. 324:461-466(1997), DiFalco et al. (Biochem. J. 326, 407-413 (1997), Meyer et al. J. Neurochem. 62, 3, 825-833 (1994), Fandl et al. (J. Biol. Chem. 269, 1, 755-759 (1994), or Luo et al. (J. Biol. Chem. 267, 17, 12275-12283 (1992), all previously cited).

This is a new rejection necessitated by applicant's amendment to the claims filed 3/23/04.

Boyce et al. is cited for the reasons set forth above. The difference between Boyce et al. and the instant claims is that Boyce does not teach the baculovirus vector comprising a heterologous gene which encodes beta-glucuronidase, neurotropin-6 (NT-6), IGF-2, brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and beta-nerve growth factor.

However, Gritson et al., Li et al., DiFalco et al., Meyer et al., Fandl et al. and Luo et al. disclose a recombinant baculovirus vector comprising the heterologous genes beta-glucuronidase, NT-6, IGF-2, BDNF, NT-3, NT-4 and beta-nerve growth factor. It would have been obvious to one of ordinary skill in the art to have inserted heterologous genes disclosed by any of Gritson, Li, DiFalco, Meyer, Fandl, or Luo, into the baculovirus disclosed by Boyce et al., since all of the references disclose the expression of heterologous genes in baculovirus vectors, and since Boyce et al. disclose the advantages of utilizing a tissue-specific, or mammalian, promoter for said expression in mammalian cells, including neuronal cells. One would have been motivated to make this construct by the known advantages of utilizing tissue specific promoters when expressing foreign genes in said tissue, as disclosed by Boyce et al. and as well known in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

TERRY MCKELVEY
PRIMARY EXAMINER